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### More childhood onset bipolar disorder in the United States than Canada or Europe

Post, Robert M.; Altshuler, Lori L.; Kupka, Ralph; McElroy, Susan L.; Frye, Mark A.; Rowe, Michael; Grunze, Heinz; Suppes, Trisha; Keck, Paul E.; Leverich, Gabriele S.

*Published in:*  
Neuroscience and Biobehavioral Reviews

*DOI:*  
[10.1016/j.neubiorev.2017.01.022](https://doi.org/10.1016/j.neubiorev.2017.01.022)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2017

[Link to publication in University of Groningen/UMCG research database](#)

*Citation for published version (APA):*

Post, R. M., Altshuler, L. L., Kupka, R., McElroy, S. L., Frye, M. A., Rowe, M., Grunze, H., Suppes, T., Keck, P. E., Leverich, G. S., & Nolen, W. A. (2017). More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention. *Neuroscience and Biobehavioral Reviews*, 74, 204-213. <https://doi.org/10.1016/j.neubiorev.2017.01.022>

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## Review article

# More childhood onset bipolar disorder in the United States than Canada or Europe: Implications for treatment and prevention<sup>☆</sup>



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## ARTICLE INFO

## Article history:

Received 11 May 2016

Accepted 18 January 2017

Available online 21 January 2017

## Keywords:

Childhood onset bipolar disorder

Depression

Substance abuse

Genetics

Epigenetics

Cohort effect

Assortative mating

Childhood adversity

Early intervention

Primary and secondary prevention

## ABSTRACT

Evidence of a high or increasing incidence of childhood onset bipolar disorder in the United States (US) has been viewed skeptically. Here we review evidence that childhood onsets of bipolar disorder are more common in the US than in Europe, treatment delays are longer, and illness course is more adverse and difficult. Epidemiological data and studies of offspring at high risk also support these findings.

In our cohort of outpatients with bipolar disorder, two of the major vulnerability factors for early onset – genetics and environmental adversity in childhood – were also greater in the US than in Europe. An increased familial loading for multiple psychiatric disorders was apparent in 4 generations of the family members of the patients from the US, and that familial burden was linked to early onset bipolar disorder. Since both early onset and treatment delay are risk factors for a poor outcome in adulthood, new clinical, research, and public health initiatives are needed to begin to address and ameliorate this ongoing and potentially devastating clinical situation.

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<sup>☆</sup> This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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## 1. Introduction

A higher incidence of childhood onset bipolar disorder in the US has most often been attributed to a variety of factors suggesting that it is artifactual rather than real. These factors have included: a broadening of the diagnosis, diagnostic differences between countries, over diagnosis, and artificial coding related to reimbursement. This skeptical view of the data has resulted in neglect of the magnitude of the problem in terms of clinical therapeutics, public health practices, and a treatment research agenda.

In this manuscript we review the evidence that much of the high incidence is very likely real and deserving of greater and multifaceted attention. The evidence reviewed includes: comparative studies of US versus European populations of patients with bipolar disorder, epidemiological studies, clinical samples, prospective follow up studies of children with a bipolar diagnosis, and studies of high risk offspring of a parent with bipolar disorder that were carried out in the US compared to non-US sites. In addition, potential reasons for the higher incidence in the US than in Europe are explored and include evidence of greater genetic vulnerability; more childhood adversity mediating psychosocial stress vulnerability; and other potential factors such as diet and higher rates of obesity with associated inflammation. Other possible contributors to the increased presence of childhood onset bipolar disorder include cohort (year of birth) and anticipation (generational) effects.

Assuming that this accumulation of evidence supports the view that many aspects of bipolar disorder present a greater problem in the US than in many other countries, several suggestions for better addressing this situation are offered. These are important to consider as more than a dozen studies (as cited below) suggest that childhood onset bipolar disorder runs a more difficult course and has a poorer outcome than adult onset illness. Multiple approaches are likely to be necessary to address the magnitude of the problem and its long-term consequences. A very extensive revision of the current treatment and research agenda will likely be necessary to begin to reverse some of the multigenerational trends for greater illness adversity in the US compared to Europe.

## 2. Types of studies and data

### 2.1. Comparative studies involving patients inside and outside of the US

Four studies directly compared patients from the US to those in Europe or Argentina.

1. In the Stanley Foundation Treatment Outcome Network (SFBN) more than 900 outpatients were recruited and followed prospectively with cross sectional and daily life chart ratings from 1995 to 2002. About 75% were bipolar I and 25% bipolar II based on SCID diagnoses (Post et al., 2014a). They came from four sites in the US (Los Angeles, Dallas, Cincinnati, and Bethesda), and from

three sites in Europe (Utrecht, the Netherlands, and Freiberg and Munich, Germany; abbreviated here as Europe). In the US versus Europe, we found onsets in childhood (before age 13) in 31.1% vs 5.6%; in adolescence (13–18) 38.1% vs. 26.6%; in young adulthood (19–29) 19.8% vs 42.2%; and in older adulthood (30 and greater) 11.0% vs 23.7%. Thus, some two thirds (69.2%) of the onsets in US adult patients with bipolar disorder started in childhood or adolescence, and only one third (32.2%) in Europe. Regarding concerns that our US sample might be non-representative, the percentage of early onset was virtually identical to that seen in the STEP-BD cohort (Perlis et al., 2004) where recruitment was from entirely different cities and academic institutions in the US than those in the SFBN (now referred to as the Bipolar Collaborative Network or BCN)

2. Bellivier et al. (2014) compared patients with bipolar disorder in the Pittsburgh case registry in the US to those from 10 different European countries. Using an admixture analysis they found a distinct increase in the youngest onset patients in the US (63%) compared to 25% in Europe, such that the average age of onset difference in this subgroup was 4.5 years.
3. Etain et al. (2012), using the same admixture analysis to define an early onset subgroup, also found that 68% of the bipolar patients in the US (from the Bipolar Phenome Database) belonged to this group in contrast to only 42% of the patients from France who were in this early onset subgroup.
4. Holtzman et al. (2015a) found a much earlier mean age of onset of bipolar disorder in the US ( $17.9 \pm 8.4$  yrs.) compared to that in Argentina ( $27.1 \pm 11.4$  years).

### 2.2. High risk offspring studies conducted in the US versus elsewhere

A substantial series of studies have examined the incidence and age of onset of bipolar disorder in the offspring of parents with bipolar disorder. Compared to those conducted elsewhere, those conducted in the US have seen more early onset bipolar disorder in the offspring followed prospectively. Exact comparisons across studies are not possible because of differences in the age range of the offspring studied and duration of follow up. However, those in the US report a percent incidence of bipolar disorder in the range of 3% to 16% (Birmaher et al., 2009b; Chang et al., 2000; Henin et al., 2005; Nurnberger et al., 2011; Singh et al., 2007; Zappitelli et al., 2011). In contrast, Duffy et al. (2007) from Canada, Wals et al. (2004) and Hillegers et al. (2005) from the Netherlands, Vandeley et al. (2012) from Switzerland, and Grigoriu-Serbanescu et al. (1989) from Romania, rarely saw bipolar onsets prior to late adolescence or early adulthood. They tend to see a temporal evolution of onsets first of anxiety disorders in the youngest children, followed by depressions, and only later bipolar disorder (Duffy et al., 2007, 2009; Hillegers et al., 2005)

Birmaher et al. (2010), while not making direct comparisons with European offspring studies, reported that the US parents with bipolar disorder had a substantial incidence of many other psychi-

atric comorbidities. These included an anxiety disorder in 72.5%, a substance abuse disorder in 63.9%, disruptive behavioral disorder in 36.9%, and ADHD in 27.5%. The high occurrence of these comorbid illnesses in the US parents with bipolar disorder could account for some of the US versus European offspring differences, as the loading of psychopathology in the parent appears related to many of the offspring illnesses.

Mesman et al. (2016) directly compared children of a bipolar parent from the US with those from the Netherlands rated on the same interview instrument, the Schedule for Affective Disorders and Schizophrenia for School Age Children (K-SADS-PL). They also evaluated dimensional psychopathology by parental reports using the Child Behavior Checklist (CBCL). They found more psychiatric comorbidities in the offspring with mood disorders from the US versus the Dutch sample (80% versus 34%; OR: 7.84,  $p < 0.001$ ), but not an earlier age of onset of bipolar disorder in that sample. However, BP-NOS was highly prevalent in the US sample and not assessed in the Dutch sample, so that the lack of difference in bipolar disorder or early onset should be viewed with caution. Surprisingly, there were no differences in the parent-reported dimensional psychopathy, such that they concluded that: “Cultural and methodological explanations for these findings warrant further study.” Their caution is mirrored by the findings of many investigators that cultural differences and other methodological factors could account for some regional diagnostic differences (Dubicka et al., 2008; Jensen-Doss et al., 2014; Mackin et al., 2006; Mesman et al., 2016; Rettew et al., 2009; Stoll et al., 1993).

In our cohort of patients with bipolar disorder, the offspring were not followed prospectively or formally diagnosed with systematic interviews. Nonetheless, the offspring of parents with bipolar disorder from the US had significantly ( $p < 0.001$ ) more depression, bipolar disorder, suicide attempts, alcohol abuse, and “other” illness than those from the Europeans (Post et al., 2016a). Overall, 46.3% of the offspring from the US had any diagnosis compared to 16.1% in those from the Netherlands and Germany.

In a 7 year prospective follow up study with formal diagnostic evaluations, Axelson et al. (Axelson et al., 2015) found a similar ratio of illnesses, but much higher incidence, such that 74% of the offspring of a US bipolar parent received a lifetime psychiatric diagnosis compared to a still-striking incidence of 48% in the community controls (also from the US). The incidences of most illnesses in the high risk offspring were strikingly higher than the controls. This included: an anxiety disorder (39.9% vs 21.8%); major depressive disorder (32.0% vs 14.9%); ADHD (30.7% vs 18.1%); disruptive behavioral disorder (27.4% vs 15.3%); substance use disorders (19.9% vs 10.1%); and any bipolar spectrum disorder, ie BP I, II, or NOS (19.2% vs 2.0%). Children initially diagnosed with depression, a disruptive behavioral disorder, or subthreshold manic symptoms (ie those with only brief bursts of mania – what they have labeled bipolar not otherwise specified or BP-NOS) were the ones most likely to convert to BP I or II upon follow up (Axelson et al., 2015).

In a 20 year follow up of offspring of a parent with unipolar depression in the US, Weissman et al. (2006) found that 83% had acquired a psychiatric diagnosis, as had 56% of the community controls. Rasic et al. (2014) in a meta-analysis found that lifetime psychiatric diagnoses in offspring of a parent with depression or bipolar disorder were higher than in controls and only slightly less prevalent than in those whose parent had schizophrenia. Bipolar disorder also occurred in the offspring of parents with schizophrenia and unipolar depression, suggesting some non-specificity of vulnerability to bipolar disorder in offspring from a parent with other illnesses beyond bipolar disorder. These data mirror those of Vandeley et al. (2012) which also showed a small percentage of

bipolar spectrum disorders in offspring of parents with unipolar disorder.

### 2.3. Epidemiological studies

Merikangas et al. (2010) reported that the incidence of a bipolar spectrum disorder in the US was 2.2% among 13–18 year olds. In their review of childhood onset bipolar disorder, Van Meter et al. (2011) reported similar incidences among a wide range of countries. However, the majority of these surveys did not include a BP-NOS category. When BP-NOS was included in the assessment, the US studies reported an average of about a 6.7% incidence, while in non-US studies the incidence averaged about 2.4%. This difference is of some consequence since the youngest patients have a high incidence of BP-NOS. Birmaher et al. (2009a) and Axelson et al. (2015) report that about 30–50% of BP-NOS children convert to BP I or BP II upon several years of follow up, and conversion is higher in those with a positive family history of bipolar disorder. The BP-NOS children were highly impaired and almost as severely ill as those with BP I and BP II, and in fact took very much longer to achieve mood stabilization (Birmaher et al., 2009a).

Merikangas et al. (2010) reported in adults a higher lifetime prevalence of bipolar spectrum disorders in the US of 4.4% compared to many other countries, including 2.3% in South American countries such as Brazil and Colombia. Since approximately two thirds of bipolar disorder in adults in the US begins in childhood or adolescence (Perlis et al., 2004; Post et al., 2014a), and there is considerable continuity of childhood with adult bipolar disorder (Geller et al., 2008), one would infer that there had to be a higher incidence in youngsters in the US than in many other countries. Similarly, Blanco et al. (2008) in the US found 12-month prevalence rates of bipolar disorder in 3.24% of college students age 19–25 and even higher rates of 4.62% in non-college students of the same age. Many of these would likely have had onsets even earlier in life. Overall, about 46% of these students had one or more psychiatric diagnoses, but only 25% were in any kind of treatment.

### 2.4. Long term prospective follow up of childhood onset bipolar disorder

Prospective naturalistic follow up studies of childhood onset illness are pertinent to the issue of US versus non-US incidence from several different perspectives. All of the longitudinal studies of young children with bipolar disorder of which we are aware emanate from US sites (Birmaher et al., 2009a; DelBello et al., 2007; Geller et al., 2008; Gitlin et al., 1995; Wozniak et al., 2011). In general, these report a considerable continuity of illness, both in terms of: a) a high level of diagnostic stability, and b) chronic persistence of symptoms during about 2/3 of the time of follow up (Geller et al., 2008). Birmaher et al. (2014) described four different groups of trajectories of illness: 1) “predominantly euthymic” (24.0%), 2) “moderately euthymic” (34.6%), 3) “ill with improving course” (19.1%), and 4) “predominantly ill” (22.3%). Those in the predominantly euthymic group 1 were characterized as being older, less severely ill at baseline, less treated with stimulants and antidepressants, and having less loading for a family history of bipolar disorder or substance abuse. Those in the predominantly ill group 4 showed essentially the opposite characteristics, including early age of onset, more severe illness at baseline, abuse in childhood, more parental illness and substance abuse, and lower socioeconomic status.

However, even in those in the best functioning group 1, despite being predominantly euthymic, “over 50% of the youths continued to experience new syndromal manic or depressive episodes, indicating that they continued to have active, clinically meaningful bipolar symptoms and the need for maintenance treatment.”



Thus, levels of severity of illness might vary over time, but the illness did not remit spontaneously, as was reported in the later onset young adults in the epidemiologically diagnosed subjects reported by Cicero et al. (2009) as discussed below.

High rates of bipolar disorder in more recent outpatient visits (Moreno et al., 2007) and in hospitalized patients (Blader and Carlson, 2007) also speak to the substantial prevalence in the US clinical population, although reservations about the contribution of differences in diagnostic practices in the US compared to elsewhere are further discussed below

### 2.5. Retrospective clinical studies and potential etiological mechanisms

Not all European countries report a dearth of childhood onset bipolar disorder. Remarkable among these reporting childhood and adolescent onsets not dissimilar to that reported in the US is Norway (which had 23% with childhood onsets in hospitalized patients (Morken et al., 2009), and 6% in an epidemiological catchment area study (Larsson et al., 2010). Soutullo et al. (2005) also reported variable rates of childhood onset bipolar disorder across different countries.

A wide variation in age of onset in different cities and countries throughout the world was reported by Bauer et al. (2014). They found that cities with the highest degrees of solar insolation (angle of the sunlight affecting its intensity) were the ones which had the earliest ages of onset of bipolar disorder. While many of those cities with a high incidence of early onsets were in the US (such as Los Angeles and San Francisco), other cities in the US (such as Miami, Princeton, and Boston) had lower solar insolation measures and later ages of onset, making it difficult to directly compare US and non-US sites.

The increased levels of obesity in the US compared to Europe (Post et al., 2014a) and their potential relationship to increases in inflammation (Goldstein and Young, 2013) also deserve further examination in relationship to early onset and a more difficult course of illness. Goldstein et al. (2008) reported that children with bipolar disorder age 7–17 were likely more obese than children in the general population and obesity was more prominent in the youngest patients. Obesity has also been linked to increases in inflammation in the brain and periphery, and increased levels of inflammatory markers have been reported in childhood onset bipolar disorder (Goldstein and Young, 2013).

### 3. Childhood onset bipolar disorder has a poorer prognosis than adult onset illness

The literature is generally consistent in the view that early onset illness has a more difficult course into adult than adult onset illness (Bellivier et al., 2014; Birmaher et al., 2014; Carlson et al., 2002; Carter et al., 2003; Ernst and Goldberg, 2004; Etain et al., 2012; Holtzman et al., 2015b; Lish et al., 1994; Mick et al., 2003; Perlis et al., 2009; Perlis et al., 2004; Post et al., 2010; Schurhoff et al., 2000). However, these studies are based either on prospective follow up studies of young children or retrospective studies in adults looking back to ages of onset in childhood.

In contrast, Cicero et al. (2009) in their analysis of two large epidemiological data sets found a peak 12 month incidence and lifetime prevalence of bipolar disorder at ages of onset of 18–20 and 21–24, but then a substantial drop off thereafter. Based on these data, they suggested that there might be a subgroup of these emerging adults with onsets of bipolar disorder that is associated with spontaneous remission. It is noteworthy that the two studies they analyzed did not interview individuals under the age of 18, so they could not examine the persistence of illness in those with

childhood and early adolescent onsets. In the retrospective studies of Post et al. (2010) and Holtzman et al. (2015b) children (<13) had even poorer outcomes in adulthood than those with adolescent onsets (<19).

Thus, the general findings in the multiple studies noted above that those with childhood onsets have a more difficult course and outcome than those with adult onsets is not incompatible with Cicero's observations that there may be spontaneous remissions in some later onset patients (age 18–24) as diagnosed in the epidemiological studies. Convergent with this viewpoint is the analysis of Goldstein and Levitt, (2006) of the National Epidemiologic Survey on Alcohol and Related Conditions which identified 1411 adults with bipolar disorder where they found that non-remitting illness was more likely in those with childhood onsets (<13 yrs) and these children also experienced longer episodes and more antisocial personality and drug use disorders.

Several factors could contribute to the poor outcome of childhood onset illness. Studies have shown that an earlier age of onset is associated with a longer delay to first treatment of either depression or mania (Morken et al., 2009; Post et al., 2010; Suominen et al., 2007; Wang et al., 2005). In our cohort of patients (average age 40 at Network entry in 1995–2002), those who reported the onsets of bipolar disorder in childhood (< age 13) experienced an average duration of delay to first treatment of more than 15 years. Those with adolescent onsets (< age 19) averaged more than a 10 years lag to first treatment, while those with adult onsets averaged 3–5 years delay (Post et al., 2010). Lish et al. (1994) and Hirschfeld et al. (2003) reported somewhat shorter delays to first treatment when they used an average duration of delay across their whole patient cohort independent of the age of onset of bipolar disorder. In a multiple regression, we found that the duration of the delay to first treatment was related to a poor prospective clinician-rated outcome independent of that related to earlier age of onset. The longer delays to first treatment were associated with longer duration and severity of depression, more ultra-rapid cycling, and less time euthymic in prospectively rated adults (Post et al., 2010).

However, two caveats about the duration of the treatment delay are noteworthy. The delay data were based on retrospective reports by adults at network entry in 1995–2002. For those reporting childhood onsets, the onsets and treatment delays represent occurrences approximately 40 years ago when bipolar disorder in children was rarely recognized. More recent data from a community health center in the years 2000–2003 suggest that delay from onset of illness to first diagnosis (and treatment) may have become much shorter, although in a small subgroup (16.7%) of the individuals the delay was still longer than 10 years (Marchand et al., 2006).

Thus, the bulk of retrospective data from multiple studies indicate that childhood onset bipolar disorder has a difficult outcome, which to some extent is further exacerbated by delay to first treatment. The poor outcome of childhood onset illness may reflect that it is an inherently more severe illness than later onset illness. . . Childhood onset illness would be occurring in an immature and developing nervous system, and the child would have the added risks of loss of social and educational opportunities. Childhood onsets also come with a considerable risk of later substance abuse, which carries further difficulties for treatment and compliance. Goldstein et al. (2013) reported a 32% rate of developing new onset of substance abuse disorder in youth diagnosed with bipolar disorder after 2.7 years of follow up. Lin et al. (2006) suggested that early onset bipolar disorder may be a distinct subtype and that early onset and substance abuse are genetically related. Further supporting the possibility that early onset is a separate genetic subtype are the data of Preisig et al. (2016) indicating that compared to adult onsets, early onset illness was more likely associated with the development of bipolar disorder in the offspring of a bipolar

parent. We also found early onset bipolar disorder in the parent conveyed increased risk of multiple illness in the offspring (Post et al., 2016a).

#### 4. Vulnerability factors

##### 4.1. The US has more genetic/familial risk factors for childhood onset bipolar disorder than the Europeans

When examining the amount of illness in the offspring of patients in the US versus the Netherlands or Germany, we looked backward 3 generations and also found each of these generations more ill than the Europeans. Compared to the Europeans, not only were our US adult patients more ill and had more poor prognosis factors (including early onset bipolar disorder, adversity in childhood, anxiety disorder comorbidity, alcohol and substance abuse, rapid cycling and more with >20 prior episodes) (Post et al., 2014a), but their parents (i.e., offspring's grandparents) and grandparents (i.e., offspring's great-grandparents) had more illness as well (Post et al., 2015a, 2016a; Post et al., 2015c). Compared to the Europeans, these illnesses in the US relatives included more depression, bipolar disorder, suicide attempts, alcohol abuse, substance abuse, and "other" illness. These grandparental and great-grandparental illnesses tended to "breed true" in offspring illness and the total burden of illness in these relatives also related to an earlier age of onset of bipolar disorder in the patients and increased occurrence of bipolar disorder in the offspring (Post et al., 2016a,b). These data again suggest vulnerability to bipolar illness may be derived from the genes not only related to bipolar disorder itself, but other illnesses as well.

In summary, in spite of the possibility of different cultural biases and methodological differences influencing some of the family history data on bipolar disorder, there is still considerable evidence of many other psychiatric illnesses occurring more frequently in 4 generations of family members of patients from the US compared to the Europeans. These preliminary findings require direct confirmation in properly controlled epidemiological studies, however. The findings of more familial loading for psychiatric illness in the US are consistent with what would be expected from the substantial incidence of childhood onset bipolar illness in the US, as virtually all of the family studies of bipolar disorder indicate greater familial loading in those with childhood compared to adult onsets (Pavuluri et al., 2004).

Assuming the findings of increased familial loading in the US over multiple generations are replicated using other methodologies, the question arises as to how this situation may have emerged. Migration of more people with traits for bipolar illness and other disorders may have occurred some generations ago. Another source of genetic vulnerability is assortative mating (for example, where one parent with depression marries another depression). A large study from Sweden finds evidence of strong assortative mating for ADHD and autistic spectrum, moderate but significant assortative mating for mood disorders, and no assortative mating for medical disorders (Nordsletten et al., 2016). In our Network we found 2–3 times more assortative mating in patients from the US than from Europe (Post et al., 2014a,b). Moreover, the spouses of the US patients had more illness than the spouses of the European patients. Thus, more assortative mating and marrying spouses with other illnesses could contribute to an increased genetic loading because of vulnerability carried by both parents (Gottesman et al., 2010; Lapalme et al., 1997; Nordsletten et al., 2016).

Another potential mechanism for increasing the gene pool for bipolar disorder and related illness has been described by Comings (1996). He presented data that a shorter time between generations (having offspring at younger ages) in those at highest risk

for psychiatric illness could in a matter of just 3 or 4 generations dramatically increase the frequency of risk genes in the general population. In accord with this possibility, the US is ranked high (46th) in having a young average age at first birth of 25 years compared to later ages at first birth in most European countries, such as 28.9 in Germany and Netherlands and 30 in the United Kingdom and Switzerland.

##### 4.2. Environmental stressors and childhood adversity are more frequent in the US than in Europe

Another major risk factor for early onset bipolar disorder is adversity in childhood in the form of verbal, physical, or sexual abuse (Brown et al., 2005; Garno et al., 2005; Leverich et al., 2007). Compared to the Europeans, patients in our Network from the US had significantly more of each type of abuse (Post et al., 2013a). More than 50% of those from the US experienced verbal abuse compared to about half that in the Europeans. While verbal abuse was most commonly also associated with concomitant physical or sexual abuse, when we examined the reported occurrence of verbal abuse alone, we found it had major effects on both early onset and a more adverse course of bipolar disorder of a magnitude similar to the occurrence of physical or sexual abuse in childhood (Post et al., 2015b). While verbal abuse is a soft indicator and subject to a variety of recall biases, including individuals who are more currently distressed viewing past interactions as more negative, the data are consistent with other findings that bullying and other forms of verbal abuse can have long lasting effects on psychopathology (De Bellis and Zisk, 2014; Teicher and Samson, 2016; Wolke and Lereya, 2015).

Other stressors occurring in the year prior to the onset of illness and prior to the latest episode before joining the Network were also greater in the US than in Europe. Stressors were lower and remained relatively stable over the course of illness in the Europeans (Post et al., 2013a). In contrast, stressors in the US were high prior to illness onset and accumulated and increased further over the course of illness (i.e., to the year prior to the last episode). These stressors were in multiple domains, including loss of social support, academic or employment difficulties, and financial and health care access problems.

A robust literature supports the viewpoint that a variety of stressors in animals and man can result in epigenetic changes, many of which could have long term to life long consequences. Epigenetic refers to "above genetics" and does not affect inherited gene sequences, but in response to environmental stimuli, chemical groups are placed on DNA or histones (around which DNA is wrapped) or alter microRNA, which in turn alter how easily genes are turned on and off or new proteins are made. We have reviewed the literature on the likely epigenetic basis of sensitization (or increased responsivity) to the recurrence of stressors, affective episodes, and bouts of substance abuse that are associated with illness progression in the recurrent mood disorders (Post, 2016). Epigenetic mechanisms are confirmed by the observations that an inhibitor of DNA methylation (zebularine), can prevent the long term effects of neonatal stress on levels of BDNF in frontal cortex and prevent the development of behavioral sensitization to repeated cocaine injections.

Epigenetic alterations can cross generations mediated by alterations in maternal or paternal behavior (Meaney et al., 2013; Weaver et al., 2004). In addition, a new mode of epigenetic trans-generational transmission has been elucidated which conveys alterations into the next generation in the absence of contact with the parents (Bale, 2014; Post, 2016; Szutorisz et al., 2014). For example, the offspring of an adult male rat that has experienced stressors or self-administered drugs of abuse will have altered stress or drug reactivity, even in the absence of any contact with

that parent. It has been shown that some epigenetic marks conveyed in gametes (sperm or ova) escape erasure and are conveyed to the next generation (Bale, 2014). Transmission to the next generation has also been shown to occur via double stranded RNA in blood affecting sperm (Chen et al., 2016; Devanapally et al., 2015).

Thus transmission of transgenerational vulnerability could potentially be conveyed by three different mechanisms: classical genetics; epigenetics based on behavioral contact; and presumably to a vastly lesser degree, gamete-mediated epigenetic transmission occurring in the absence of contact. Based on the available data, it would appear that those from the US would potentially be more vulnerable to illness based on any or all three of these mechanisms (Post, 2016). These data would have important clinical implications, as they would suggest that the situation in the US could have consequences for future generations and is not likely to be self-correcting.

#### 4.3. Cohort and anticipation effects add to the childhood onset problem

The pessimistic view of more genetic and epigenetic-based vulnerability to illness of future generations in the US compared to the Europeans is further bolstered by two

other time trends or secular phenomena; a cohort (year of birth) effect and an anticipation (generational) effect. The cohort effect suggests that every birth cohort from the beginning of the 1900s has had an increased incidence and earlier age of onset of both unipolar depression and bipolar disorder (Hirschfeld and Weissman, 2002; Kessler et al., 2007; Lange and McInnis, 2002; Post et al., 2016b; Visscher et al., 2001). The mechanisms involved in the cohort effect, which has been demonstrated in many countries, are not known, but are likely multifactorial (Visscher et al., 2001). In addition, there may also be cohort effects for ADHD and substance abuse (Kessler et al., 2007), which could contribute to vulnerability in future generations.

The anticipation effect refers to the phenomena seen most clearly in neurological illnesses such as Huntington's chorea (HC) where the age of onset of illness may be much earlier in the offspring than the parental generation. Both genetic (such as expansion of triple repeat sequences in HC) and non-genetic mechanisms of anticipation in bipolar disorder have been suggested.

Taken together these two different time trend or secular effects in the general population further signal that the problems of early onset unipolar and bipolar disorder may be becoming more prevalent and problematic.

#### 4.4. Untoward results of inadequately treated bipolar disorder

This literature about the consequences of less-than-ideal treatment has been reviewed in detail elsewhere (Post and Leverich, 2008), but a few summary points are worthy of mention here. The high rates of dysfunction, disability, and suicide in bipolar disorder are well known. Less well known are the effects of accumulating numbers of episodes or duration of illness on cognitive dysfunction, treatment refractoriness, loss of cortical volume, and development of dementia in old age (Post et al., 2012). The estimates of years of premature loss of life expectancy of individuals with serious psychiatric disorders is a staggering 1–3 decades depending on an individuals residence in a specific state in the US (Colton and Manderscheid, 2006; Newcomer and Hennekens, 2007). This degree of loss of life expectancy is based more on cardiovascular disease than from suicide.

### 5. Clinical and public health implications and preliminary recommendations

One way of beginning to address the burgeoning problem of childhood onset bipolar and related disorders is to begin to accept the reality and magnitude of the problem. While the precise percentages of illness in the US compared to Europe may vary across studies and differ to some extent in subsequent replication studies, the effects as reviewed here appear to be large, consistent across multiple studies and methodologies, and internally consistent with genetic and environmental vulnerability factors. Until this acceptance in the scientific and public community occurs, approaches to the problems are likely to be desultory and inadequate. For example, James et al. (2014) in examining hospitalization discharge diagnoses in the US versus the United Kingdom found a 72.1 fold increase for pediatric bipolar disorder and a 7.2 fold increase for adult bipolar disorder, as well as a 13.2 fold increase for ADHD. They concluded that the differences in the rates of pediatric bipolar disorder may be due to differences in diagnostic practices.

While differences in diagnostic practices could account for some of the differences in hospitalization rates, they do not address the phenomenally huge degrees of psychiatric morbidity that these numbers represent. The rate of 100.9 hospitalizations per 100,000 population for childhood onset bipolar disorder in the US compared to 1.4/100,000 in England is astounding. That represents a lot of very sick children being hospitalized in the US even if there are some ambiguities about the diagnostic labeling.

In addition, in the study of James et al. (2014) differences in diagnostic practices for pediatric bipolar disorder would not account for the 13.2 fold increases in discharge diagnoses for ADHD in children or the 7.2 fold increases in adult bipolar disorder in the US versus England. While the data reviewed here may have some confounds of diagnostic differences in the US versus Europe that require further study, the number of hospitalizations for something resembling pediatric bipolar disorder in the US is alarming. This is especially true since the very large literature reviewed above indicates that compared to adult onset (or even late adolescent onset), childhood onset bipolar disorder represents a more severe illness with a poorer outcome in adulthood.

When Banks et al. (2006) found that US compared to British while males ages 55–74 had small but statistically significantly higher frequencies of most medical illnesses adjusted for all confounders, they did not mince words and concluded that “American adults are less healthy than Europeans at all wealth levels.” The differences in pediatric bipolar or bipolar-like admissions in the US versus Britain are astoundingly large and merit recognition as such. Despite the caveats about cultural differences in diagnostic practice, it would appear prudent to recognize the enormous burden, and tentatively conclude that American children are very likely less healthy than Europeans.

In addition, given the breath of the existent data from so many different methodologies that we have reviewed (including comparative studies, high risk offspring studies, clinical populations, prospective follow up studies, and epidemiological data that includes BP-NOS), one would hope that a reflexive response of “we need more data”, be replaced with “given the enormous magnitude of the problem and implications for the health, well being, and longevity of current and future generations, we must take action.”

One might suggest a health education campaign as a good place to start. McGorry and colleagues in Australia have made great strides in the area of early recognition and treatment in those with pre-psychotic symptoms or prodromal schizophrenia. This is noteworthy from the multiple perspectives of destigmatization, public and political buy in, health care access, community involvement in clinical trials, and initial positive results with psychotherapeutic intervention and perhaps treatment with omega 3 fatty acids



(Amminger et al., 2015). If this kind of initiative can be done with prodromal schizophrenia, it certainly could be with early onset depression and bipolar disorder where the need is vastly greater in terms of the less than 1% incidence of schizophrenia compared to the 2–3% incidence of bipolar disorder and the 10 fold higher percent with depression.

One needs to develop other early recognition strategies. In this direction one could better inform high risk groups (parents with a history of depression or bipolar disorder who have young children) to be cognizant of their child's mood and behavior, and if major problems emerge to seek help for their child. As we have seen from the data above, the saying “psychiatric illness runs in families” could be promulgated and acted upon as it is in so many other medical illnesses. If the risk of psychiatric illness in one parent is added to by illness in the other parent (Gottesman et al., 2010; Lapalme et al., 1997; Nordsletten et al., 2016), and multigenerational histories of psychiatric illness are also present (Post et al., 2015a,b, 2016a; Weissman et al., 2006), additional vigilance about illness in the offspring may be indicated. Certainly these genetic/familial vulnerabilities, in concert with the occurrence of childhood adversity and prodromal symptoms and syndromes, should further heighten awareness (Post et al., 2013b). Efforts could be directed at the public, pediatricians, and primary care physicians, as well as psychiatrists who could be encouraged to ask about the health of their adult patients' children. If a child is highly symptomatic and other resources are not available (which is all too common), these adult psychiatrists could consider initiating treatment.

Advocacy groups should also be encouraged to teach their members about the high risk status of children of parents with mood and related disorders and to endorse evaluation and treatment seeking in instances of social and educational impairment, rather than rather than the current typical mode of hoping the behaviors will be self correcting and just go away. Ghaemi et al. (2003) emphasize the admonition of “first do no harm” in relationship to the use of antidepressants in bipolar depression, and many would extend this in general to treatment of childhood onset bipolar disorder. However, ignoring the treatment of severely ill and dysfunctional children with psychiatric illness would appear more related to stigma, and in some ways would in fact represent doing harm. This educational effort could also extend to support groups and to peer specialists who have increasingly important roles in advocacy groups such as the Depression and Bipolar Support Alliance (DBSA).

One action that parents could take immediately is to begin to longitudinally chart the severity of dysfunction associated with the common symptoms of childhood psychiatric illness. A secure online rating device is available from the Child Network, which can be accessed at [www.bipolarnews.org](http://www.bipolarnews.org), click on Child Network. After a brief one time demographics questionnaire and a longer symptom check list, parents are sent an email reminder every Sunday to briefly rate the severity of symptoms of depression, anxiety, ADHD, oppositional behavior, and mania and to list any psychosocial or drug treatment.

Such weekly ratings can be printed out graphically and taken to physicians in order to better visualize the course, severity, and consistency of symptoms in order to more easily evaluate the need for treatment and treatment effectiveness, if any is initiated.

When patients and family members are aware of the numerical values of blood glucose, blood pressure, cholesterol, and weight, more effective approaches to diabetes and cardiovascular disease are facilitated, and well-being and longevity are accordingly enhanced. Similarly, longitudinal numerical or graphic monitoring of a child's illness behaviors will facilitate earlier recognition and more effective treatment. A cogent demonstration of this is reported by Kessing et al. (2013). They randomized youngsters with a first hospitalization for mania to 2 years of specialty clinic treatment versus treatment as usual (TAU). Specialty clinic treatment

included: post-hospital transition counseling; psycho-education; symptom recognition and monitoring; psychotherapy; and pharmacotherapy. Not only were there markedly fewer relapses initially over the first 2 years in the specialty clinic group, but these differences persisted and were magnified over the subsequent 4 years even though all patients had returned to TAU after 2 years.

These data together with a large number of controlled studies showing superior effects of randomized psychotherapy/psycho-education compared to TAU in children and adults with bipolar disorder (Scott et al., 2007; Swartz and Swanson, 2014; Vallarino et al., 2015) provide strong evidence for the benefits of multi-modal psychotherapeutic and pharmacological treatment. Moreover, Miklowitz et al. (2013) found that family focused treatment (FFT) was superior to treatment as usual (TAU) in children with a diagnosis of depression, BP-NOS, or cyclothymia who also had a positive family history of bipolar disorder (in a parent or sibling). FFT includes illness education, monitoring, therapy, and enhanced within family communication. The effects of FFT on depressive, anxious, and manic symptoms were largest in families with highest levels of expressed negative emotion. Nadkarni and Fristad (2010) reported that therapy might be able to prevent the conversion of depression to bipolar disorder in high risk children. Other psychotherapeutic work with families has also proved effective (Fristad et al., 2009; Pavuluri et al., 2004).

The NIMH could hold conferences about the most effective way of changing attitudes and fostering new initiatives. Certainly, increased attention to the sparse portfolio of treatment-related studies is indicated (Post, 2009; Post and Kowatch, 2006). Special initiatives to encourage study of these illnesses in childhood should be fostered and funded. When such a national initiative was enacted to foster and fund studies of schizophrenia many decades ago, dramatic increases in treatment studies for that illness rapidly followed. A similar program is now needed to reverse the ongoing dearth of treatment studies of both childhood and adult bipolar and related disorders.

A treatment effectiveness network to acquire systematic data from children being treated in clinical practice, like that available for oncology patients treated in clinical practice situations organized by the National Cancer Institute, could help to more rapidly generate needed treatment and prevention data. The need for these kinds of data is highlighted by the findings of Findling et al. (2007) that divalproex sodium was no more effective than placebo in preventing dropout from the study for any reason in 56 youth with BP-NOS or cyclothymia and the presence of one parent with bipolar disorder. Interestingly, youth with a higher family loading discontinued earlier than those with less family loading. These findings of no significant effect of divalproex, contrast with the positive effects of family focused therapy in a similar group of at risk youth (Miklowitz et al., 2013). Practical comparative clinical trials using randomized open data could rapidly provide guidance about best treatment strategies (Post and Kowatch, 2006).

Shonkoff and Garner (2012) have advocated for pediatricians to become the primary guardians of children's health. They emphasize that toxic stress in childhood (verbal, physical, and sexual abuse or neglect) is a major cause of both medical and psychiatric illnesses in adulthood. Most children with psychiatric problems are seen by pediatricians and other primary care physicians (Anderson et al., 2015), so enhanced efforts in the training of these non-specialists for adequate recognition, treatment, or referral is indicated.

Hudziak et al. (2014) have campaigned for increased attention to child health and brain development. They suggest universal efforts for encouraging exercise, mindfulness, music, and meditation (each of which has demonstrated positive effects on brain structure or function) in school-aged children. In those who are at high risk or who are already symptomatic, more intensive or specialized treatment could be offered on top of these general measures.



Given the magnitude and consequences of the problems of child health involved, it appears that very broad and multifaceted approaches are needed to begin to reduce and prevent these prevalent illnesses in both high risk children and in children in the general population in the US. Some possible first approaches are outlined here, but more innovative, comprehensive, and long term clinical, research, and public health strategies are also required.

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